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APPLICATION FOR UNITED STATES LETTERS PATENT

for

**STENTS AND METHODS FOR PREPARING STENTS FROM
WIRES HAVING HYDROGEL COATING LAYERS THEREON**

by

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5 **STENTS AND METHODS FOR PREPARING STENTS FROM WIRES
 HAVING HYDROGEL COATING LAYERS THEREON**

FIELD OF THE INVENTION

 The present invention relates to radially expandable stents for use
10 in humans or animals.

BACKGROUND

 Radially expandable stents are widely used medical devices. A
stent typically is a cylindrically shaped device formed from wire(s) or a
15 tube and intended to act as a permanent prosthesis. A typical stent
ranges from about 5 millimeters to about 50 millimeters in length. A stent
is deployed in a body lumen from a radially compressed configuration
into a radially expanded configuration that allows it to contact and support
a body lumen. Optionally, a balloon of appropriate size and pressure can
20 be used to open a lesion prior to delivery of the stent to its intended
location.

 It is known in the art of fabricating medical devices to coat stents
with coating materials chosen to impart a variety of desirable properties
to the device. For example, coatings have been applied to stents to
25 improve mechanical properties and to provide for drug release and for
biocompatibility. Since fabrication of a radially expandable stent from
wire requires the wire to be mechanically bent a multitude of times, it is
generally preferred to apply the coating to the prefabricated stent to avoid
the resultant coating breaks and adhesion failures that frequently result
30 from bending a precoated wire. As a result, the costs for applying
coatings to prefabricated stents, along with the resulting coating quality,
are largely controlled and limited by the fact that a batch process is being
used to coat irregularly shaped objects.

 A few reports of the fabrication of stents from wires that have been
35 precoated with specific polymeric layers have appeared in the art, some

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examples of which may be found in the issued U.S. Patents listed in
Table 1 below.

Table 1: Prior Art Patents

	<u>Patent No.</u>	<u>Inventor(s)</u>	<u>Issue Date</u>
5	6,113,621	Wiktor	5 September 2000
	6,106,454	Berg et al.	22 August 2000
	6,100,474	McGregor et al.	8 August 2000
	6,077,413	Hafeli et al.	20 June 2000
10	5,980,551	Summers et al.	9 November 1999
	5,968,091	Pinchuk et al.	19 October 1999
	5,865,814	Tuch	2 February 1999
	5,843,158	Lenker et al.	1 December 1998
	5,837,313	Ding et al.	17 November 1998
15	5,837,008	Berg et al.	17 November 1998
	5,824,048	Tuch	20 October 1998
	5,776,184	Tuch	7 July 1998
	5,722,984	Fischell et al.	3 March 1998
	5,679,400	Tuch	21 October 1997
20	5,624,411	Tuch	29 April 1997
	5,607,463	Schwartz et al.	4 March 1997
	5,591,224	Schwartz et al.	7 January 1997
	5,554,181	Das	10 September 1996
	5,545,211	An et al.	13 August 1996
25	5,527,354	Fontaine et al.	18 June 1996
	5,525,356	Jevne et al.	11 June 1996
	5,464,650	Berg et al.	7 November 1995
	5,449,372	Schmaltz et al.	12 September 1995
	5,356,433	Rowland et al.	18 October 1994
30	5,336,518	Narayanan et al.	9 August 1994
	5,330,500	Song	19 July 1994
	5,163,958	Pinchuk	17 November 1992

20 The present invention has certain objects. That is, various
embodiments of the present invention provide solutions to one or more
problems existing in the prior art respecting radially expandable stents for
use in animals or humans. Those problems include inadequate
mechanical properties, lack of coating uniformity, surface roughness,
25 undesirable drug release properties, and inadequate biocompatibility.
Various embodiments of the present invention have the object of solving
at least one of the foregoing problems. While some radially expandable
stents were capable of solving at least some of the foregoing problems,
they were generally not employed because of their prohibitively high cost
30 or difficult manufacturing processes. It is therefore another object of the
present invention to provide an improved radially expandable stent that

may be manufactured and sold at low cost, yet still fulfill at least one of the foregoing objects.

In comparison to known radially expandable stents, various embodiments of the present invention may provide one or more of the following advantages. The present invention provides radially expandable stents with improved properties over stents known in the art. For example, stents of the present invention are preferably provided with a substantially uniform hydrogel coating layer thereon. Coating uniformity may be important in preventing complications such as clotting that occurs during use when uncoated wire surfaces of the stent are exposed to blood.

The present invention also provides advantageous methods for producing such stents. Methods of the present invention allow the wire to be coated by a continuous process. Such continuous coating processes may provide economic advantages as well as product quality improvements. For example, continuous coating methods of the present invention preferably provide substantially uniform coatings with low surface roughness. Low surface roughness may be desirable for handling and inserting the stent into the body, and may also contribute to the reduction of blood clotting that is observed when the surface of a stent is exposed to bodily fluids such as blood.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As used herein, "substantially uniform coating" means that the wire surface is completely covered by the coating. Preferably the stent has a coating with a uniform dry thickness of at least about 0.1 micrometer and more preferably at least about 5 micrometers. Preferably the stent has a coating with a uniform dry thickness of at most about 25 micrometers and more preferably at most about 10 micrometers. Preferably the stent has a dry coating thickness with a relative standard deviation of no greater than about 10 percent.

active agents also include, for example, biologically active molecules (biomolecules) such as drugs.

As used herein, "modifying cellular response" means increasing, decreasing, causing, or eliminating a response by cells to a disease, an injury, or a foreign body.

In one aspect, the present invention provides a radially expandable stent that includes a wire having a hydrogel coating layer thereon. Preferably the coating layer is substantially uniform. More preferably the stent has a hydrogel coating layer with an average dry coating thickness (T) of about 0.1 micrometer to about 25 micrometers, a standard deviation (), and a relative standard deviation ($100 \times / T$) of no greater than about 10 percent. The hydrogel coating layer may optionally include a biologically active agent. The coating layer preferably provides a hydrophilic, biocompatible surface.

In another aspect, the present invention provides a method for preparing a radially expandable intravascular stent, and stents that are preparable and, preferably, prepared by such a method. The method includes providing a metal wire; applying to the wire a solution that includes a solvent and a water soluble polymer in the solvent; evaporating the solvent to provide a polymeric coating on the wire; crosslinking the polymeric coating to provide a hydrogel coating layer on the wire; and fabricating the coated wire into a cylindrical, radially expandable stent body. Preferably the solution is applied to the wire by a continuous coating method such as, for example, passing the wire through the solution at a substantially constant speed. The hydrogel coating layer may optionally be swollen with water prior to fabricating the coated wire into a stent.

In another aspect, the present invention provides a method for delivery of a biologically active agent to the interior of a body lumen. In one embodiment, the method includes providing a metal wire; applying to the wire a solution that includes a solvent, a water soluble polymer in the solvent, and a biologically active agent dispersed in the solvent;

evaporating the solvent to provide a polymeric coating on the wire;
crosslinking the polymeric coating to provide a hydrogel coating layer on
the wire; fabricating the coated wire into a cylindrical, radially expandable
stent body; introducing the stent body transluminally into a selected
5 portion of the body lumen; and radially expanding the stent body into
contact with the body lumen. In another embodiment, the method
includes providing a metal wire; applying to the wire a solution that
includes a solvent and a water soluble polymer in the solvent;
evaporating the solvent to provide a polymeric coating on the wire;
10 crosslinking the polymeric coating to provide a hydrogel coating layer on
the wire; fabricating the coated wire into a cylindrical, radially expandable
stent body; applying a biologically active agent to the hydrogel coating
layer; introducing the stent body transluminally into a selected portion of
the body lumen; and radially expanding the stent body into contact with
15 the body lumen.

In another aspect, the present invention provides a method of
modifying cellular response in a body lumen to a disease, injury, or
foreign body. In one embodiment, the method includes providing a metal
wire; applying to the wire a solution that includes a solvent, a water
20 soluble polymer in the solvent, and a biologically active agent dispersed
in the solvent; evaporating the solvent to provide a polymeric coating on
the wire; crosslinking the polymeric coating to provide a hydrogel coating
layer on the wire; fabricating the coated wire into a cylindrical, radially
expandable stent body; introducing the stent body transluminally into a
25 selected portion of the body lumen; radially expanding the stent body into
contact with the body lumen; and controllably releasing the biologically
active agent into the body lumen. In another embodiment, the method
includes providing a metal wire; applying to the wire a solution that
includes a solvent and a water soluble polymer in the solvent;
30 evaporating the solvent to provide a polymeric coating on the wire;
crosslinking the polymeric coating to provide a hydrogel coating layer on
the wire; fabricating the coated wire into a cylindrical, radially expandable

stent body; applying a biologically active agent to the hydrogel coating
layer; introducing the stent body transluminally into a selected portion of
the body lumen; radially expanding the stent body into contact with the
body lumen; and controllably releasing the biologically active agent into
5 the body lumen.

The present invention provides novel radially expandable stents
and methods for fabricating such stents. A water soluble polymer is
coated onto a wire, the solvent is evaporated, and the polymer is
crosslinked to provide a hydrogel coating layer on the wire. The coated
10 wire is then fabricated into a stent. Preferably the water soluble polymer
is coated onto the wire using a continuous coating process. Continuous
solution coating processes are capable of providing substantially uniform
coatings, resulting in stents with improved coating uniformity compared to
coated stents known in the art.

15 Wire useful for articles and methods of the present invention
includes drawn low-memory level material such as stainless steel,
titanium ASTM F63-83 Grade 1, and high carat gold K 19-22. Copper
alloy (e.g., 110) when properly coated with polyester or
poly(tetrafluoroethylene) can also be used. Titanium and gold are
20 biocompatible, inert, and require no special treatment. Preferably the
wire is stainless steel or tantalum. The diameter of the wire is preferably
about 50 micrometers to about 200 micrometers.

Optionally the wire may be pretreated or precoated with, for
example, gold, ceramics, polymers, and vapor deposited materials. For
25 example, a wire may be precoated with a polysulfone to promote
adhesion of a hydrogel coating layer. A polysulfone precoating layer may
be applied, for example, by any suitable solvent coating and drying
method. If a polymer is used as the pretreatment layer, the resulting dry
coating thickness is preferably about 0.01 micrometer to about 1
30 micrometer.

A "hydrogel" is 3-dimensional network of cross-linked, hydrophilic
macromolecules capable of being swelled and incorporating about 20

percent to about 95 percent water by weight. Hydrogel coating may be prepared by coating a solution of a water soluble polymer, and then crosslinking the polymeric coating. The crosslinking reaction may occur during a drying step or as a separate step.

- 5 Hydrogel coating solutions useful for articles and methods of the present invention include a water soluble polymer dissolved, dispersed, or suspended in a solvent to provide a coating solution. Optionally, the coating solution may contain other functional and/or non-functional additives including, but not limited to, initiators, crosslinking agents,
- 10 biologically active agents, and polymers with functional groups. Preferably the coating solution includes at least about 1 percent by weight polymer and more preferably at least about 10 percent by weight polymer. Preferably the coating solution includes at most about 90 percent by weight polymer and more preferably at most about 25 percent
- 15 by weight polymer.

- Hydrogel coatings useful for articles and methods of the present invention may be selected by using appropriate screening tests. Such exemplary tests include a coil test. In such a test, a coated wire is coiled around a stainless steel wire of 2 mm thickness that is being rotated at
- 20 100 revolutions per minute. The resulting coil of coated wire is then visually analyzed using light microscopy at a 50 power magnification. The coated wire may be tested as either in the dried state or in the swollen state that results from immersion in a fluid, preferably an aqueous fluid such as, for example, saline or water. Coatings tested in
- 25 the swollen state that show no visible cracks using this coiling method are considered mechanically stable and suitable as wire coatings for stents and methods of the present invention. Preferably the coatings show no visible cracks when tested in the dry state using this coiling method.

- 30 Polymers that may be used to prepare hydrogel coatings useful for articles and methods of the present invention preferably have substantial flexibility. Flexibility may arise from the use of a polymer with a low T_g , for

- Solvents useful in coating solutions for articles and methods of the present invention include solvents that can be removed from the coated wire at drying temperatures of about 50°C to about 200°C. Useful solvents generally have a boiling point of about 40°C to about 200°C. Solvents useful in coating solutions of the present invention include, for

example, tetrahydrofuran, acetone, ethanol, isopropanol, water,
methylene chloride, chloroform, hexane, heptane, xylenes, and toluene.

Crosslinking agents may optionally be added to the coating
solution to modify the physical and chemical properties of the dried
5 coating as desired. Suitable crosslinking agents include, but are not
limited to, functional, multifunctional, and polyfunctional materials,
including, for example, acrylate, acrylamide, or epoxide functionalities.
When crosslinking agents are used, they are typically added in about 0.1
percent by weight to about 50 percent by weight based on the weight of
10 the polymer.

When crosslinking agents are used in the solvent coating, initiators
may be added to facilitate crosslinking. For example, when polyacrylate
crosslinking agents are used, a free-radical generating initiator may be
included. Suitable free-radical generating initiators may be activated by
15 light or heat. Preferred initiators include, for example, ammonium
persulfate. When initiators are used, they are typically added in about
0.0001 percent by weight to about 0.01 percent by weight based on the
weight of the monomer.

Coating methods known in the art may be used to apply the
20 coating solution to the wire for articles and methods of the present
invention. Preferably the method is a continuous coating method. A
particularly useful method for applying coatings for articles and methods
of the present invention is to pass a wire at a substantially constant
speed through the coating solution. For example, the wire may be pulled
25 in a vertical direction from the solution to provide a substantially uniform
coating. Optionally, the wire may be passed through a die to remove
excess coating. When using continuous coating methods, useful coating
speeds will depend on factors such as the percent solids of the coating
solution, viscosity of the coating solution, and temperature of the coating
30 solution. Preferably the wire may be coated at about 1 lineal meters per
minute to about 100 lineal meters per minute. The temperature of the

coating solution may be maintained at any temperature desired, for example, at 25°C.

After the coating is applied, it may be dried by methods known in the art. Suitable drying methods include, but are not limited to, conduction drying, convection drying, hot air impingement, steam treatment, infrared irradiation, ultraviolet irradiation, and microwave irradiation. Preferably the coating is dried by the application of heat. Preferably the coated wire is dried with air at a temperature of about 50°C to about 200°C for about 0.01 second to about 100 seconds.

Preferably the coating is applied so as to result in a dry coating thickness of at least about 0.1 micrometer and preferably at least about 5 micrometers. Preferably the coating is applied so as to result in a dry coating thickness of at most about 25 micrometers and more preferably at most about 10 micrometers.

Preferably the coating and drying methods are selected so as to provide a substantially uniform coating. Adequate uniformity may be determined by visually inspecting the coated wire to ensure that no uncoated wire is exposed. Alternatively, surface uniformity of the coating may be measured by field emission spectrometry (FEM), with a substantially uniform coating showing complete coverage of the wire.

Preferably the coating and drying methods are selected so as to provide a coating with a substantially uniform thickness as measured by the standard deviation (). Preferably for a coating of dry thickness T , the relative standard deviation ($100 \times \text{standard deviation} / T$) is no greater than about 10 percent.

Preferably the coating and drying methods are selected so as to provide a coating with low surface roughness. Surface roughness may be measured using, for example, laser profilometry. Preferably the relative surface roughness ($100 \times R_q / T$) is at most about 25 percent and more preferably at most about 10 percent. Alternatively, the surface roughness may be qualitatively evaluated by microscopic examination. Generally, the uncoated wire surface visually appears to have a rougher

surface than the coated surface when coated by the method of the
present invention. Preferably the coating has low surface roughness as
evidenced by sharp edges being substantially absent. Moreover, wire
used for articles and methods of the present invention need not be
5 polished in order to obtain stents with good surface roughness properties.

For some applications it is preferable that the coating be swellable
when immersed in fluids, preferably aqueous fluids such as, for example,
saline or water. For coatings containing biologically active agents, for
example, swelling of the coating in bodily fluids will enhance the release
10 of the biologically active agents. The rate and degree of swelling may be
chosen to provide the desired release properties.

The solvent coated wire can be fabricated into a radially
expandable stent by methods known in the art. For example, U.S. Pat.
No. 4,886,062 (Wiktor) discloses a vascular stent and a method for
15 preparing the stent. Initially a wire is preformed by folding into a two-
dimensional zig-zag pattern, typically a sinusoidal pattern. A length of
the patterned wire under little or no tension is then wound around a
mandrel, and the mandrel removed to provide a radially expandable
stent. The fabrication may be carried out with dried or wet coatings. If
20 desired, the fabrication can be carried out by folding the wire while the
wire is immersed in a solution. For example, when using hydrogel
coatings, it is useful to fabricate the stent with the wire immersed in water
to maintain the hydrogel coating in the wet or swollen state. Alternatively,
the solvent coated wire may also be fabricated into stents using other
25 techniques known in the art.

Biologically active agents may be added to coated radially
expandable stents of the present invention by adding the biologically
active agent to the coating solution or by applying the biologically active
agent to the coated hydrogel layer. If the biologically active agent is
30 applied to the coated hydrogel layer, the application may take place
either before or after the coated wire has been fabricated into a stent as
desired. The biologically active agent may be applied to the hydrogel

coating in either the dry or the wet state. Application of the biologically active agent to the hydrogel coating in the wet or swollen state is preferred for incorporating the biologically active agent more uniformly throughout the coating. Suitable application methods include, for example, dip coating. Biologically active agents may be added to stents to provide, for example, biocompatible surfaces. Useful biologically active agents include, but are not limited to, dipyridamole, heparin, anti-platelet drugs, anti-thrombogenic drugs, anti-proliferative drugs, and anti-mitotic drugs. When biologically active agents are used, they are typically added in about 0.1 percent by weight to about 25 percent by weight based on the weight of the polymer.

Coatings used in the stents and methods of the present invention may be selected and formulated to controllably release biologically active agents at the desired rate. The rate of release may depend on, for example, the amount and type of biologically active agent present in the coating and the temperature and conditions of the desired release. The rate of release may also depend on the properties of the selected polymer including, for example, solubility and polarity. Other factors may also effect the rate of release including, for example, crosslink density.

The surface coated radially expandable stents of the present invention may also be used for immobilizing biologically active agents. For example, when polyacrylamide is used as the wire coating, an amide-functional surface is obtained. The amide functional surface may be converted to an amine-functional surface by the Hoffman degradation process as described in copending U.S. Pat. Application Serial No. 09/245,834 filed 8 February 1999 entitled "METHOD FOR ATTACHMENT OF BIOMOLECULES TO SURFACES THROUGH AMINE-FUNCTIONAL GROUPS." Biologically active agents (e.g., periodate-activated heparin, collagen) may be readily coupled to the amine-functional surface. See, for example, U.S. Pat. Nos. 5,607,475 and 5,679,659.

Biologically active agents may be attached in an appropriate amount and orientation effective to provide, for example, an improved nonthrombogenic surface relative to the substrate without the biologically active agent. The present invention provides relatively high biologically
5 active agent loading capacities (often as high as 50 micrograms of biologically active agents per square centimeter of modified surface) and bioactivities (often as high as 1.0 International Unit (IU) thrombin (IIa) deactivated per square centimeter of modified surface).

The present invention is illustrated by the following examples. It is
10 to be understood that the particular examples, materials, amounts, and procedures are to be interpreted broadly in accordance with the scope and spirit of the invention as set forth herein.

EXAMPLES

15 Hydroxyethyl methacrylate (HEMA, 99.9 percent purity) was obtained from Kodak (Rochester, NY). Electrophoresis grade acrylamide (99.9 percent purity was obtained from Aldrich Chemicals Inc. (Milwaukee, WI). Polyvinylpyrrolidone (povidone, PVP, Average M_w ca. 1,300,000 daltons was obtained from Aldrich Chemicals Inc. (Milwaukee,
20 WI). Ammonium persulfate was obtained from from Aldrich Chemicals Inc. (Milwaukee, WI). Deionized water was used for all reactions.

Example 1

A solution of poly(hydroxyethyl methacrylate) is prepared by free
25 radical polymerization of hydroxyethyl methacrylate (20 percent by weight) in water using ammonium persulfate initiator (up to 0.01 percent by weight) at 50°C. Prior to use as a coating solution, a bis-acrylate is added up to a concentration of about 0.01 percent by weight.

Example 2

30 A solution of polyacrylamide is prepared by free radical polymerization of acrylamide (20 percent by weight) in water using

weight, and an initiator was added up to a concentration of about 0.01 percent by weight. Unfractionated heparin (Diosynth, Oss, NL) was added to the solution at a concentration of up to 5 percent by weight. Stainless steel wires and tantalum wires were coated and dried as described in Example 4 to give a dry coating thickness of 5 micrometers.

Pieces of wire were incubated with a solution of phosphate buffered saline at 37°C. Samples were taken over time and assayed for heparin activity via determination of the rate of inactivation of a thrombin-antithrombin III mixture. It was concluded that approximately 15 percent of the heparin that was incorporated in the coating was released within 2 hours. Additional incubation of the coating resulted in a much slower release (10 percent in two days).

Example 6

A solution of poly(vinyl pyrrolidone) was prepared by dissolving PVP (20 percent by weight) in water. Prior to use as a coating solution, vinyl pyrrolidone was added up to a concentration of about 5 percent by weight, and an initiator was added up to a concentration of about 0.01 percent by weight. Dipyridamole (Merck, Darmstadt, GDR) was added to the solution at a concentration of up to 20 percent by weight. Stainless steel wires and tantalum wires were coated and dried as described in Example 4 to give a dry coating thickness of 5 micrometers.

Pieces of wire were incubated with phosphate buffered saline (pH=7.4) at 37°C. The solution was assayed periodically using ultraviolet-visible spectrometry. During the first 90 minutes approximately 20 percent of the drug was released. This burst was followed by release at a much slower rate. Additional incubation of the wire during a period of two days gave an additional release of 10 percent.

Example 7

Stainless steel wires and tantalum wires were coated with PVP and dried as described in Example 4 to give a dry coating thickness of

approximately 4 micrometers. Pieces of coated wire were incubated with a Na_2CO_3 buffer (pH=10) at 60°C for one hour to induce hydrolysis of some of the vinyl pyrrolidone rings. After thorough rinsing, the pieces were soaked in a solution of 0.5 percent by weight poly(allylamine) (Mw = 5 1500, Aldrich), in a 0.25M 4-morpholineethanesulfonic acid solution (pH=5.5) containing 0.05M 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. The reaction was allowed to proceed for one hour at room temperature after which the samples were rinsed with deionized water.

10 A solution of unfractionated heparin (5 mg/ml) in 0.05M phosphate buffer (pH=6.88) was prepared. NaIO_4 (0.065 mg/ml, Aldrich) was added to the solution to induce periodate oxidation for introduction of aldehyde groups into the heparin chains. The reaction was allowed to proceed for 3 hours at room temperature.

15 The resulting solution was diluted 1:5 by volume with 0.4M acetate buffer (pH=4.66). NaBH_3CN (0.4 mg/ml, Aldrich) was added and the aminated samples were incubated with the resulting periodate oxidized heparin solution for 18 hours at room temperature. The samples were then rinsed with deionized water, 1 M NaCl, and deionized water again.

20 Staining of the samples with Toluidine blue revealed an abundance of immobilized heparin.

Incubation of the heparinized samples with a solution of antithrombin III resulted in adsorbed activated antithrombin III that was capable of deactivation of thrombin when contacted with a solution 25 containing the latter. This showed that the immobilized heparin was bioactive.

The complete disclosure of all patents, patent applications, and publications, and electronically available material cited herein are 30 incorporated by reference.

The preceding specific embodiments are illustrative of the practice of the invention. It is to be understood, therefore, that other expedients

known to those skilled in the art or disclosed herein, may be employed
without departing from the invention or the scope of the appended claims.
For example, the present invention is not limited to methacrylate,
acrylamide, or poly(vinyl pyrrolidone) based hydrogel coated stents. The
5 present invention is also not limited to hydrogel coated stents *per se*, but
may find further applications such as, for example, biocompatible medical
devices. The present invention further includes within its scope methods
of making and using the stents described hereinabove.

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